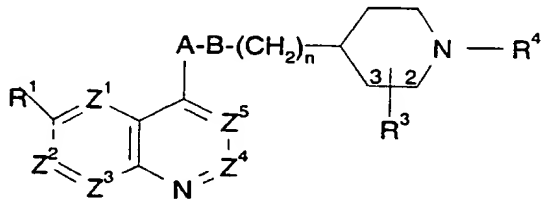
PIPERIDINYLQUINOLINES AS PROTEIN TYROSINE KINASE INHIBITORS

This invention relates to novel medicaments, being novel antibacterial compounds and compositions.

WO9217475, WO9802438, WO9703069 and WO9639145 disclose certain bicyclic heteroaromatic compounds having cholinesterase inhibitor, protein tyrosine kinase inhibitor, cell proliferation inhibitor and human epidermal growth factor receptor type 2 inhibitor activity.

This invention provides a method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment of an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

one of Z^1, Z^2, Z^3, Z^4 and Z^5 is N or CR^{1a} and the remainder are CH;

R^1 is selected from hydroxy; (C_{1-6}) alkoxy optionally substituted by (C_{1-6})alkoxy, amino, piperidyl, guanidino or amidino optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, NH_2CO, hydroxy, thiol, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted (C_{1-6})alkyl; halogen; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethyl; nitro; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, or when one of Z^1, Z^2, Z^3, Z^4 and Z^5 is N, R^1 may instead be hydrogen;

R^{1a} is selected from hydrogen and the groups listed above for R^1;

R^3 is in the 2- or 3-position and is:

carboxy; (C_{1-6})alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{1-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R^{10}; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R^{10}; or 5-oxo-1,2,4-oxadiazol-3-yl; or

R^3 is in the 2- or 3-position and is (C_{1-4})alkyl or ethenyl substituted with any of the groups listed above for R^3 and 0 to 2 groups R^{12} independently selected from:

thiol; halogen; (C_{1-6})alkylthio; trifluoromethyl; azido; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl; amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; oxo; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

provided that when R^3 is disubstituted with hydroxy or amino and carboxy containing substituents these may optionally together form a cyclic ester or amide linkage, respectively;

and provided that R^3 is other than (C_{1-4})alkyl or ethenyl substituted by (C_{1-6})alkoxycarbonyl or aminocarbonyl optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl and 0 to 2 groups R^{12};

wherein R^{10} is selected from (C_{1-4})alkyl; (C_{2-4})alkenyl; aryl; a group R^{12} as defined above; carboxy; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{1-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; cyano; or tetrazolyl;

R^4 is a group $-CH_2-R^5$ in which R^5 is selected from:
(C_{3-12})alkyl; hydroxy(C_{3-12})alkyl; (C_{1-12})alkoxy(C_{3-12})alkyl; (C_{1-12})alkanoyloxy(C_{3-12})alkyl; (C_{3-6})cycloalkyl(C_{3-12})alkyl; hydroxy-, (C_{1-12})alkoxy- or (C_{1-12})alkanoyloxy-(C_{3-6})cycloalkyl(C_{3-12})alkyl; cyano(C_{3-12})alkyl; (C_{2-12})alkenyl; (C_{2-12})alkynyl; tetrahydrofuryl; mono- or di-(C_{1-12})alkylamino(C_{3-12})alkyl; acylamino(C_{3-12})alkyl; (C_{1-12})alkyl- or acyl-aminocarbonyl(C_{3-12})alkyl; mono- or di-(C_{1-12})alkylamino(hydroxy) (C_{3-12})alkyl; optionally substituted phenyl(C_{1-2})alkyl, phenoxy(C_{1-2})alkyl or phenyl(hydroxy)(C_{1-2})alkyl; optionally substituted diphenyl(C_{1-2})alkyl; optionally substituted phenyl(C_{2-3})alkenyl; optionally substituted benzoyl or benzoylmethyl; optionally substituted heteroaryl(C_{1-2})alkyl;and optionally substituted heteroaroyl or heteroaroylmethyl;

n is 0, 1 or 2;

either A-B is NHC(O)NH or NHC(O)O, or

A is NR^{11}, O, $S(O)_x$ or CR^6R^7 and B is NR^{11}, O, $S(O)_x$ or CR^8R^9 where x is 0, 1 or 2 and wherein:
each of R^6 and R^7 R^8 and R^9 is independently selected from: H; thiol; (C_{1-6})alkylthio; halo; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{1-6})alkenyl;
or R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined;
or R^6 and R^8 together represent –O- and R^7 and R^9 are both hydrogen;
or R^6 and R^7 or R^8 and R^9 together represent oxo;
and each R^{11} is independently H, trifluoromethyl, (C_{1-6})alkyl, (C_{1-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, $(C_{1-}$

6)alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{1-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{1-6})alkenyl;

provided that A and B cannot both be selected from NR^{11}, O and $S(O)_x$ and when one of A and B is CO the other is not CO, O or $S(O)_x$.

In one aspect the invention provides a method according to the invention wherein in compounds of formula (I) R^1 and R^{1a} are selected from the groups listed above other than trifluoromethyl.

The invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

The invention also provides a pharmaceutical composition for use in the treatment of bacterial infections in mammals comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

Preferably Z^5 is CH or N and Z^1-Z^4 are each CH.

In a preferred aspect, when A is CH_2 or CHOH and B is CH_2 or A is CH_2 and B is CHOH and n is 1 the substitutents at the 3- and 4-position of the piperidine ring are cis.

When R^1 or R^{1a} is substituted alkoxy it is preferably C_{2-6} alkoxy substitituted by optionally N-substituted amino, guanidino or amidino, or C_{1-6}alkoxy substituted by piperidyl. Suitable examples of R^1 alkoxy include methoxy, n-propyloxy, i-butyloxy, aminoethyloxy, aminopropyloxy, aminopentyloxy, guanidinopropyloxy, piperidin-4-ylmethyloxy, phthalimido pentyloxy or 2-aminocarbonylprop-2-oxy. Preferably R^1 is methoxy, amino- or guanidino-(C_{3-5})alkyloxy, guanidino(C_{3-5})alkyloxy, piperidyl(C_{3-5})alkyloxy, nitro or fluoro, most preferably methoxy.

R^{1a} is preferably hydrogen.

R^3 preferably contains carboxy, cyano or 2-oxo-oxazolidinyl optionally substituted by R^{10}.

Where R^3 is substituted alkyl is it preferably substituted methyl.

Examples of R^3 include CO_2H, CH_2CO_2H, $(CH_2)_2CO_2H$, $(CH_2)_2CN$, $CONH_2$, $CH(OH)CH_2CN$, $CH(OH)CH_2CO_2H$, $CH{=}CHCO_2H$ or 2-oxo-oxazolidinyl.

R^3 is preferably in the 3-position.

R^3 is most preferably CH_2CO_2H or 2-oxo-oxazolidinyl.

Preferably A is NH, NCH_3, O, CH_2, CHOH, $CH(NH_2)$, C(Me)(OH) or CH(Me).

Preferably B is CH_2, CHOH or CO.

Preferably n is 0 or 1.

More preferably:

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when A is NH, B is CO and n is 1 or 0;
when A is O, B is CH_2 and n is 1 or 0;
when A is CH_2 or CH_2OH, B is CH_2, and n is 1 or 0;
when A is NCH_3, $CH(NH_2)$, C(Me)(OH) or CH(Me), B is CH_2 and n is 1;
when A is CR^6R^7 and B CR^8R^9 and R^6 and R^8 together represent –O- and R^7 and R^9 are both hydrogen and n is 1.

$AB(CH_2)_n$ is most preferably $(CH_2)_3$.

Suitable groups R^4 include n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-dodecyl, methoxybutyl, phenylethyl, phenylpropyl or 3-phenyl-prop-2-en-yl optionally substituted on the phenyl ring, 3-benzoylpropyl, 4-benzoylbutyl, 3-pyridylmethyl, 3-(4-fluorobenzoyl)propyl, cyclohexylmethyl, cyclobutylmethyl, t-butoxycarbonylaminomethyl and phenoxyethyl.

Preferably R^4 is (C_{5-10})alkyl, unsubstituted phenyl(C_{2-3})alkyl or unsubstituted phenyl(C_{3-4})alkenyl, more preferably hexyl, heptyl, 5-methylhexyl, 6-methyl heptyl, 3-phenyl-prop-2-en-yl or 3-phenylpropyl, most preferably n-heptyl.

Most preferably R^5 is unbranched at the α and, where appropriate, β positions.

Halo or halogen includes fluoro, chloro, bromo and iodo.

The term 'heterocyclic' as used herein includes aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or substituted by, for example, up to three groups selected from optionally substituted amino, halogen, (C_{1-6})alkyl, (C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy, carboxy, carboxy salts, carboxy esters such as (C_{1-6})alkoxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryl, and oxo groups. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Compounds within the invention containing a heterocyclyl group may occur in two or more tautometric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

Where an amino group forms part of a single or fused non-aromatic heterocyclic ring as defined above suitable optional substituents in such substituted amino groups include (C_{1-6})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, thiol, (C_{1-6})alkylthio, halo or trifluoromethyl, and amino-protecting groups such as acyl or (C_{1-6})alkylsulphonyl groups.

The term 'heteroaryl' includes the aromatic heterocyclic groups referred to above. Examples of heteroaryl groups include pyridyl, triazolyl, tetrazolyl, indolyl, thienyl, isoimidazolyl, thiazolyl, furanyl,quinolinyl, imidazolidinyl and benzothienyl.

When used herein the term 'aryl', includes phenyl and naphthyl, each optionally substituted with up to five, preferably up to three, groups selected from halogen, mercapto, (C_{1-6})alkyl, phenyl, (C_{1-6})alkoxy, hydroxy(C_{1-6})alkyl, mercapto (C_{1-6})alkyl, halo(C_{1-6})alkyl, hydroxy, optionally substituted amino, nitro, carboxy, (C_{1-6})alkylcarbonyloxy, (C_{1-6})alkoxycarbonyl, formyl, or (C_{1-6})alkylcarbonyl groups.

The term 'acyl' includes (C_{1-6})alkoxycarbonyl, formyl or (C_{1-6}) alkylcarbonyl group.

Compounds of formula (I) wherein R^3 is other than (C_{1-6})alkoxycarbonyl; optionally substituted aminocarbonyl, CN or COOH, hereinafter 'compounds of formula (IA)' and pharmaceutically acceptable derivatives thereof are novel and as such form part of the invention.

The invention also provides a pharmaceutical composition comprising a compound of formula (IA), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

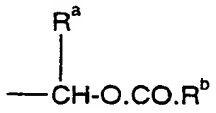
Some of the compounds of this invention may be crystallised or recrystallised from solvents such as organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the formula (I) or salt thereof.

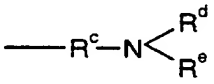
Pharmaceutically acceptable derivatives of the above-mentioned compounds of formula (I) include the free base form or their acid addition or quaternary ammonium salts, for example their salts with mineral acids e.g. hydrochloric, hydrobromic, sulphuric nitric or phosphoric acids, or organic acids, e.g. acetic, fumaric, succinic, maleic, citric, benzoic, p-toluenesulphonic, methanesulphonic, naphthalenesulphonic acid or tartaric acids. Compounds of formula (I) may also be prepared as the N-oxide. Compounds of formula (I) having a free carboxy group may also be prepared as an *in vivo* hydrolysable ester. The invention extends to all such derivatives.

Examples of suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming groups include those forming esters which break down readily in the human

body to leave the parent acid or its salt. Suitable groups of this type include those of part formulae (i), (ii), (iii), (iv) and (v):



(I)



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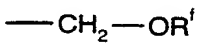

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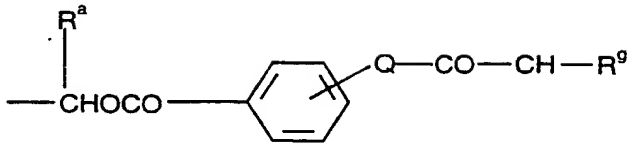

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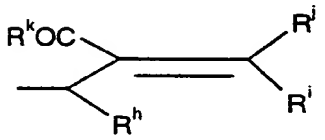


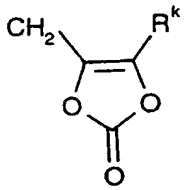
(V)

wherein R^a is hydrogen, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, methyl, or phenyl, R^b is (C_{1-6}) alkyl, (C_{1-6}) alkoxy, phenyl, benzyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyloxy, (C_{1-6}) alkyl (C_{3-7}) cycloalkyl, 1-amino (C_{1-6}) alkyl, or 1-$(C_{1-6}$ alkyl)amino (C_{1-6}) alkyl; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups; R^c represents (C_{1-6}) alkylene optionally substituted with a methyl or ethyl group and R^d and R^e independently represent (C_{1-6}) alkyl; R^f represents (C_{1-6}) alkyl; R^g represents hydrogen or phenyl optionally substituted by up to three groups selected from halogen, (C_{1-6}) alkyl, or (C_{1-6}) alkoxy; Q is oxygen or NH; R^h is hydrogen or (C_{1-6}) alkyl; R^i is hydrogen, (C_{1-6}) alkyl optionally substituted by halogen, (C_{2-6}) alkenyl, (C_{1-6}) alkoxycarbonyl, aryl or heteroaryl; or R^h and R^i together form (C_{1-6}) alkylene; R^j represents hydrogen, (C_{1-6}) alkyl or (C_{1-6}) alkoxycarbonyl; and R^k represents (C_{1-8}) alkyl, (C_{1-8}) alkoxy, (C_{1-6}) alkoxy(C_{1-6})alkoxy or aryl.

Examples of suitable *in vivo* hydrolysable ester groups include, for example, acyloxy(C_{1-6})alkyl groups such as acetoxymethyl, pivaloyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, and (1-aminoethyl)carbonyloxymethyl; (C_{1-6})alkoxycarbonyloxy(C_{1-6})alkyl groups, such as

ethoxycarbonyloxymethyl, α-ethoxycarbonyloxyethyl and propoxycarbonyloxyethyl; di(C_{1-6})alkylamino(C_{1-6})alkyl especially di(C_{1-4})alkylamino(C_{1-4})alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; 2-((C_{1-6})alkoxycarbonyl)-2-(C_{2-6})alkenyl groups such as 2-(isobutoxycarbonyl)pent-2-enyl and 2-(ethoxycarbonyl)but-2-enyl; lactone groups such as phthalidyl and dimethoxyphthalidyl.

A further suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming group is that of the formula:



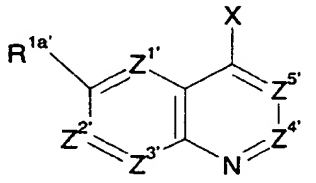
wherein R^k is hydrogen, C_{1-6} alkyl or phenyl.

R is preferably hydrogen.

Certain of the above-mentioned compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. For examples the invention includes compound in which an A-B group $CH(OH)-CH_2$ is in either isomeric configuration, the *R*-isomer is preferred. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

In a further aspect of the invention there is provided a process for preparing compounds of formula (IA), or a pharmaceutically acceptable derivative thereof, which process comprises:

(a) reacting a compound of formula (IV) with a compound of formula (V):



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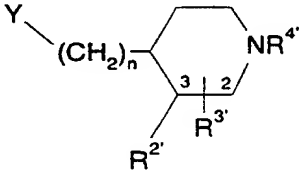


(V)

wherein Z^1, Z^2, Z^3, Z^4 and Z^5, m, n, R^1, R^2, R^3 and R^4 are as defined in formula (I), and X and Y may be the following combinations:

(i) X is M and Y is $CH_2CO_2R^x$

(ii) X is CO_2R^y and Y is $CH_2CO_2R^x$

(iii) one of X and Y is $CH=SPh_2$ and the other is CHO

(iv) X is CH_3 and Y is CHO

(v) X is CH_3 and Y is CO_2R^x

(vi) X is $CH_2CO_2R^y$ and Y is CO_2R^x

(vii) X is $CH=PR^z_3$ and Y is CHO

(viii) X is CHO and Y is $CH=PR^z_3$

(ix) X is halogen and Y is $CH=CH_2$

(x) one of X and Y is COW and the other is $NHR^{11'}$ or NCO

(xi) one of X and Y is $(CH_2)_p$-V and the other is $(CH_2)_qNHR^{11'}$, $(CH_2)_qOH$, $(CH_2)_qSH$ or $(CH_2)_qSCOR^x$ where p+q=1

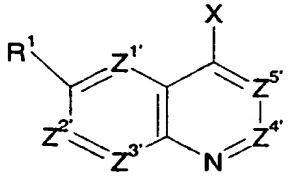
(xii) one of X and Y is CHO and the other is $NHR^{11'}$

(xiii) one of X and Y is OH and the other is $-CH=N_2$

in which V and W are leaving groups, R^x and R^y are (C_{1-6})alkyl and R^z is aryl or (C_{1-6})alkyl, or

(xiv) X is NCO, Y is OH or NH_2 ;

(b) reacting a compound of formula (IV) with a compound of formula (Vb):



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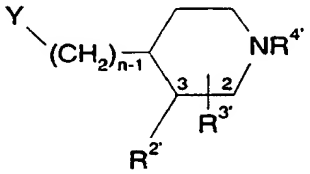
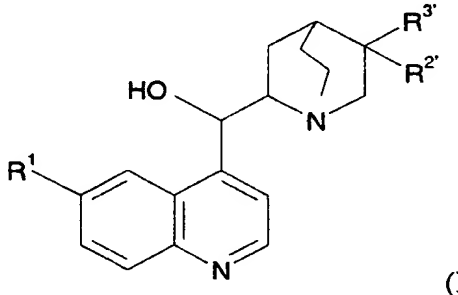


(Vb)

wherein Z^1, Z^2, Z^3, Z^4 and Z^5, m, n, R^1, R^2, R^3 and R^4 are as defined in formula (I), X is $CH_2NHR^{11'}$ and Y is CHO or COW or X is CH_2OH and Y is $-CH=N_2$;

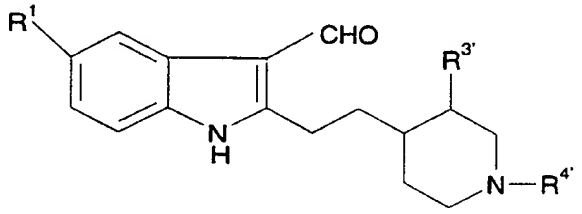
(c) rearranging a compound of formula (II):



(II)

to give a compound of formula (III) which is a compound of formula (I) where Z^1-Z^5 are CH, n is 1, A-B is $COCH_2$ and R^2 is H, or a compound of formula (VII) which is a compound of formula (I) where n is 1, A-B is $CHOHCH_2$ or CH_2CHOH and R^2 is H; or

(d) photooxygenating a compound of formula (VI):



(VI)

in which $Z^{1'}$-$Z^{5'}$ are Z^1-Z^5 or groups convertible thereto, $R^{11'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ are R^{11}, R^1, R^2, R^3 and R^4 or groups convertible thereto, and thereafter optionally or as necessary converting $R^{11'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ to $R^{11'}$, R^1, R^2, R^3 and R^4, converting $Z^{1'}$-$Z^{5'}$ to Z^1-Z^5, converting A-B to other A-B, interconverting R^{11}, R^1, R^2, R^3 and/or R^4 and forming a pharmaceutically acceptable derivative thereof.

Process variants (a)(i) and (a)(ii), (c) in certain aspects and (d) initially produce compounds of formula (I) where A-B is $COCH_2$. The products of variants (c) and (d) have n=1.

Process variant (a)(iii) and (c) in other aspects initially produces compounds of formula (I) wherein A-B is CH_2CHOH or $CHOHCH_2$.

Process variant (a)(iv) initially produces compounds of formula (I) wherein A-B is CH_2CHOH. .

Process variants (a)(v) and (a)(vi), initially produce compounds of formula (I) wherein A-B is CH_2CO.

Process variants (a)(vii), (a)(viii) and (a)(ix) initially produce compounds where A-B is CH=CH.

Process variant (a)(x) initially produces compounds of formula (I) wherein A-B is $CONHR^{11}$ or $NHR^{11}CO$.

Process variant (a)(xi) initially produces compounds of formula (I) wherein one of A and B is CH_2 and the other is NHR^{11}, O or S.

Process variant (a)(xii), initially produce compounds of formula (I) wherein A-B is CH_2NHR^{11} or $NHR^{11}CH_2$.

Process variant (a)(xiii) initially produces compounds of formula (I) wherein A-B is OCH_2 or CH_2O.

Process variant (a)(xiv) initially produces compounds of formula (I) where A-B is NHC(O)NH or NHC(O)O.

Process variant (b) initially produces compounds of formula (I) wherein A is CH_2 and B is NHR^{11} or O.

In process variant (a)(i) M is preferably an alkali metal, more preferably Li. The reaction is conducted in an aprotic solvent preferably THF, ether or benzene at -78 to 25°C. An analogous route is described in G. Grethe et al (1972) Helv. Chimica.Acta., 55, 1044.

In process variant (a)(ii) the process is two step: firstly a condensation using a base, preferably sodium hydride or alkoxide, sodamide, alkyl lithium or lithium dialkylamide, preferably in an aprotic solvent e.g. ether, THF or benzene; secondly, hydrolysis using an inorganic acid, preferably HCl in aqueous organic solvent at 0-100°C. Analogous routes are described in DE330945, EP31753, EP53964 and H. Sargent, J. Am. Chem. Soc. **68**, 2688-2692 (1946).

In process variant (a)(iii) if a base is used it is preferably NaH, KH, an alkyl lithium e.g. BuLi, a metal alkoxide e.g. NaOEt, sodamide or lithium dialkylamide e.g.di-isopropylamide. An analogous method is described in US 3989691 and in Taylor et al. (1972) JACS 94, 6218)

In process variant (a)(iv) the reaction is carried out in the presence of a base, preferably organometallic or metal hydride e.g. NaH, lithium diisopropylamide or NaOEt, preferably in an aprotic solvent, preferably THF, ether or benzene at -78 to 25°C (analogous process in Gutswiller et al. (1978) JACS 100, 576).

In process variant (a)(v) the reaction is carried out in the presence of a base, preferably organometallic or metal hydride e.g. NaH, lithium diisopropylamide or NaOEt, preferably in an aprotic solvent, preferably THF, ether or benzene at -78 to 25°C. An analogous method is described in US 3772302.

In process variant (a)(vi) a similar Claisen methodology to that described for (a)(ii) is used, analogous to that described in Soszko et. al., Pr.Kom.Mat. Przyr.Poznan.Tow.Przyj.Nauk., (1962), 10, 15.

In process variants (a)(vii) and (viii) if a base is used it is preferably NaH, KH, an alkyl lithium e.g. BuLi, a metal alkoxide e.g. NaOEt, sodamide or lithium dialkylamide e.g.di- isopropylamide. An analogous method is described in US 3989691 and M.Gates et. al. (1970) J. Amer.Chem.Soc., 92, 205, as well as Taylor et al. (1972) JACS 94, 6218.

In process variant (a)(ix) the reaction is carried out using palladium catalysis. The palladium catalyst is preferably palladium acetate in the presence of trialkyl or triaryl phosphine and a trialkylamine e.g. triphenyl phosphine and tributylamine. An analogous method is described in S. Adam et. al. (1994) Tetrahedron, 50, 3327.

In process variant (a)(x), or (b) where Y is COW,the reaction is a standard amide formation reaction:

1. Activation of a carboxylic acid (e.g., to an acid chloride, mixed anhydride, active ester, O-acyl-isourea or other species), and treatment with an amine (Ogliaruso, M. A.; Wolfe, J. F. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Acid Derivatives, Pt. 1* (John Wiley and Sons, 1979), pp 442-8; Beckwith, A. L. J. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Amides (Ed. Zabricky, J.)* (John Wiley and Sons, 1970), p 73 ff. The acid and amide are preferably reacted in the presence of an activating agent such as 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1-hydroxybenzotriazole (HOBT),

2. Aminolysis of esters (Suzuki, K.; Nagasawa, T. in *Encyclopedia of Reagents for Organic Synthesis (Ed. Paquette, L. A.)* (John Wiley and Sons, 1995), p 5188 and refs. cited therein.)

3. The specific methods of:

a. *in situ* conversion of an acid into the amine component by a modified Curtius reaction procedure (Shioiri, T.; Murata, M.; Hamada, Y., *Chem. Pharm. Bull.* **1987**, *35*, 2698)

b. *in situ* conversion of the acid component into the acid chloride under neutral conditions (Villeneuve, G. B.; Chan, T. H., *Tet. Lett.* **1997**, *38*, 6489).

In process variant (b) a final reduction step provides the required amine.

In process variant (a)(xi) where one of X and Y contains NHR^{11} the leaving group V is halogen and the reaction is a standard amine formation reaction such as direct alkylation described in (Malpass, J. R., in *Comprehensive Organic Chemistry,* Vol. 2 (Ed. Sutherland, I. O.), p 4 ff.) or aromatic nucleophilic displacement reactions (see references cited in *Comprehensive Organic Chemistry,* Vol. 6, p 946-947 (reaction index); Smith, D. M. in *Comprehensive Organic Chemistry*, Vol. 4 (Ed. Sammes, P. G.) p 20 ff.). This is analogous to the methods described in GB 1177849.

In process variant (a)(xi) where one of X and Y contains OH or SH, this is preferably converted to an OM or SM group where M is an alkali metal by treatment of an alcohol, thiol or thioacetate with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium, or, for SH, metal alkoxide such as sodium methoxide. The X/Y group containing the thioacetate $SCOR^x$ is prepared by treatment of an alcohol or alkyl halide with thioacetic acid or a salt thereof under Mitsunobu conditions. The leaving group V is a halogen. The reaction may be carried out as described in Chapman et.al., J. Chem Soc., (1956),1563, Gilligan et. al., J. Med. Chem., (1992), **35**, 4344, Aloup et. al., J. Med. Chem. (1987), **30**, 24, Gilman et al., J.A.C.S. (1949), **71**, 3667 and Clinton et al., J.A.C.S. (1948), **70**, 491, Barluenga et al., J. Org.

Chem. (1987) **52**, 5190. Alternatively where X is OH and Y is CH_2V, V is a hydroxy group activated under Mitsunobu conditions (Fletcher et.al. J Chem Soc. (1995), 623).

In process variants (a)(xii) and (b) where Y is CHO the reaction is a standard reductive alkylation using, e.g., sodium triacetoxyborohydride (Gribble, G. W. in *Encyclopedia of Reagents for Organic Synthesis (Ed. Paquette, L. A.)* (John Wiley and Sons, 1995), p 4649).

In process variant (a)(xiii), or (b) where X is CH_2OH and Y is $-CH=N_2$, the reaction is as described in den Hertzog et. al., recl.Trav. Chim. Pays-Bas, (1950),**69**, 700.

In process variant (a)(xiv) the reaction of the compounds of formulae (IV) and (V) is a standard urea or carbamate formation reaction conducted by methods well known to those skilled in the art (for example see March, J; *Advanced Organic Chemistry, Edition 3* (John Wiley and Sons, 1985)). The process is preferably carried out in a polar, non-nucleophilic solvent such as N,N-dimethylformamide.

In process variant (c) the rearrangement may be effected by treatment with an acid, preferably an organic acid such as acetic acid and the reaction temperature is 80-120°C. Alternatively the compound of formula (II) is quaternised by treatment with an alkylating agent and treated with base such as KOH to give, depending upon the stereochemistry of the OH and the nature of the quaternery salt and base, either the ketone of formula (III) or an epoxide which can be opened to the alcohol of formula (VII by reduction (see EP0035821).

In process variant (d) the reaction is preferably carries out in an alcohol, preferably methanol under irradiation conditions which are known to generate singlet oxygen as described in M. Ihara et.al. (1988), J.Chem Soc Perkin Trans. 1, 1277.

Reduction of A or B CO to CHOH can be readily accomplished using reducing agents well known to those skilled in the art, e.g. sodium borohydride in aqueous ethanol or lithium aluminiun hydride in ethereal solution.. This is analogous to methods described in EP 53964, US 384556 and J. Gutzwiller et. al. (1978) J.Amer.Chem.Soc., 100, 576.

The carbonyl group A or B may be reduced to CH_2 by treatment with a reducing agent such as hydrazine in ethylene glycol at 130-160°C in the presence of potassium hydroxide.

Reaction of a carbonyl group A or B with an organometallic reagent yields a group where R^6 or R^8 is OH and R^7 or R^9 is alkyl.

A hydroxy group in A or B may be oxidised to a carbonyl group by oxidants well known to those skilled in the art ; for example, manganese dioxide, pyridinium chlorochromate or pyridinium dichromate.

An A-B group $COCH_2$ may be converted to COCH-halogen, by treating the ketone or a derivative with a halogenating agent, reduced to CHOHCHCl and then converted to the epoxide which may in turn be reduced to CH_2CHOH.

Methods for conversion of CH=CH by reduction to CH_2CH_2 are well known to those skilled in the art, for example using hydrogenation over palladium on carbon as catalyst. Methods for conversion of CH=CH to give the A-B group as $CHOHCH_2$ or CH_2CHOH are well known to those skilled in the art for example by epoxidation and subsequenct reduction by metal hydrides, hydration, hydroboration or oxymercuration.

A hydroxyalkyl group A-B CH_2CHOH or $CHOHCH_2$ may be dehydrated to give the group CH=CH by treatment with an acid anhydride such as acetic anhydride.

An amide group $CONHR^{11'}$ or $NHR^{11'}CO$ may be reduced to the amine using a reducing agent such as lithium aluminium hydride

A ketone group may be converted to an amide CONH via the oxime by a Beckmann rearrangement (Ogliaruso, M.A.; Wolfe, J. F., *ibid.* pp 450-451; Beckwith, A. L. J., *ibid.* pp 131 ff.)

A hydroxy group in A or B may be converted to azido by activation and displacement e.g. under Mitsunobu conditions using hydrazoic acid or by treatment with diphenylphosphorylazide and base, and the azido group in turn may be reduced to amino by hydrogenation.

A sulphur group A or B may be converted to the sulphoxide $S(O)_x$ by oxidation with peracids or a wide range of oxidants known to those skilled in the art (see Advanced Organic Chemistry *(Ed. March, J.)* (John Wiley and Sons, 1985), p 1089 and refs. cited therein).

$R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ are preferably R^1, R^2, R^3 and R^4. $R^{1'}$ is preferably methoxy. $R^{2'}$ is preferably hydrogen. $R^{3'}$ is preferably vinyl or contains a carboylate ester group. $R^{4'}$ is preferably H, R^4 or a protecting group.

Conversions of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ and interconversions of R^1, R^2, R^3 and R^4 are conventional. In compounds which contain an optionally substituted hydroxy group, suitable conventional hydroxy protecting groups which may be removed without disrupting the remainder of the molecule include acyl and alkylsilyl groups.

For example $R^{1'}$ methoxy is convertible to $R^{1'}$ hydroxy by treatment with lithium and diphenylphosphine (general method described in Ireland et. al. (1973) J.Amer.Chem.Soc.,7829) or HBr. Alkylation of the hydroxy group with a suitable alkyl derivative bearing a leaving group such as halide and a protected amino, piperidyl, amidino or guanidino group or group convertible thereto, yields, after conversion/deprotection, R^1 C_{1-6}alkoxy substituted by optionally N-substituted amino, piperidyl, guanidino or amidino.

Examples of $Z^{1'}$-$Z^{5'}$ are $CR^{1a'}$ where $R^{1a'}$ is a group convertible to R^{1a}.

$R^{3'}$ alkenyl is convertible to hydroxyalkyl by hydroboration using a suitable reagent such as 9-borabicyclo[3.3.1]nonane, epoxidation and reduction or oxymercuration.

$R^{3'}$ 1,2-dihydroxy can be prepared from $R^{3'}$ alkenyl using osmium tetroxide or other reagents well known to those skilled in the art (see Advanced Organic Chemistry *(Ed. March, J.)* (John Wiley and Sons, 1985), p 732-737 and refs. cited therein) or epoxidation followed by hydrolysis (see Advanced Organic Chemistry *(Ed. March, J.)* (John Wiley and Sons, 1985), p 332,333 and refs. cited therein).

Opening an epoxide $R^{3'}$ group with cyanide anion yields a $CH(OH)-CH_2CN$ group.

Opening an epoxide-containing $R^{3'}$ group with azide anion yields an azide derivative which can be reduced to the amine. Conversion of the amine to a carbamate is followed by ring closure with base to give the 2-oxo-oxazolidinyl containing R^3 group.

Substituted 2-oxo-oxazolidinyl containing R^3 groups may be prepared from the corresponding aldehyde by conventional reaction with a glycine anion equivalent, followed by cyclisation of the resulting amino alcohol (M Grauert et al, Ann Chem (1985) 1817, Rozenberg et al, Angew Chem Int Ed Engl (1994) 33(1) 91). The resulting 2-oxo-oxazolidinyl group contains a carboxy group which can be converted to other R^{10} groups by standard procedures.

Carboxy groups within R3 may be prepared by Jones' oxidation of the corresponding alcohols CH_2OH using chromium acid and sulphuric acid in water/methanol (E.R.H. Jones et al, J.C.S. 1946,39). Other oxidising agents may be used for this transformation such as sodium periodate catalysed by ruthenium trichloride (G.F.Tutwiler *et al*, J.Med.Chem., 1987, *30*(6), 1094), chromium trioxide-pyridine (G. Just *et al*, Synth. Commun. 1979, *9*(7), 613), potassium permanganate (D.E.Reedich *et al*, J. Org. Chem.,1985,*50*(19),3535, and pyridinium chlorochromate (D. Askin *et al*, Tetrahedron Letters, 1988, 29(3), 277.

The carboxy group may alternatively be formed in a two stage process, with an initial oxidation of the alcohol to the corresponding aldehyde using for instance dimethyl sulphoxide activated with oxalyl chloride (N.Cohen *et al*, J. Am. Chem. Soc., 1983, 105, 3661) or dicyclohexylcarbodiimide (R.M.Wengler, Angew. Chim. Int. Ed. Eng., 1985, 24(2), 77), or oxidation with tetrapropylammonium perruthenate (Ley *et al*, J. Chem.Soc. Chem Commun.,1987, 1625). The aldehyde may then be separately oxidised to the corresponding acid using oxidising agents such as silver (II) oxide (R.Grigg *et al*, J. Chem. Soc. Perkin1,1983, 1929), potassium permanganate (A.Zurcher, Helv. Chim. Acta., 1987, 70 (7), 1937), sodium periodate catalysed by ruthenium trichloride (T.Sakata

et al, Bull. Chem. Soc. Jpn., 1988, 61(6), 2025), pyridinium chlorochromate (R.S.Reddy *et al*, Synth. Commun., 1988, 18(51), 545) or chromium trioxide (R.M.Coates *et al*, J. Am. Chem. Soc.,1982, 104, 2198).

An R^3 CO_2H group may also be prepared from oxidative cleavage of the corresponding diol, $CH(OH)CH_2OH$, using sodium periodate catalysed by ruthenium trichloride with an acetontrile-carbontetrachloride-water solvent system (V.S.Martin *et al*, Tetrahedron Letters, 1988, *29*(22), 2701).

R^3 groups containing a cyano or carboxy group may also be prepared by conversion of an alcohol to a suitable leaving group such as the corresponding tosylate by reaction with para-toluenesulphonyl chloride (M.R.Bell, J. Med. Chem.,1970, 13, 389), or the iodide using triphenylphosphine, iodine, and imidazole (G. Lange, Synth. Commun., 1990, 20, 1473). The second stage is the displacement of the leaving group with cyanide anion (LA.Paquette et al, J. Org. Chem.,1979, 44 (25), 4603; P.A.Grieco et al, J. Org. Chem.,1988, 53 (16), 3658). Finally acidic hydrolysis of the nitrile group gives the desired acids (H.Rosemeyer et al, Heterocycles, 1985, 23 (10), 2669). The hydrolysis may also be carried out with base e.g. potassium hydroxide (H.Rapoport, J. Org. Chem.,1958, 23, 248) or enzymatically (T. Beard et al, Tetrahedron Asymmetry, 1993, 4 (6), 1085).

Other functional groups in R^3 may be obtained by conventional conversions of carboxy or cyano groups.

Tetrazoles are conveniently prepared by reaction of sodium azide with the cyano group (e.g. F. Thomas et al, Bioorg. Med. Chem. Lett., 1996, *6* (6), 631; K.Kubo et al, J. Med. Chem., 1993, 36,2182) or by reaction of azidotri-n-butyl stannane with the cyano group followed by acidic hydrolysis (P.L.Ornstein, J. Org. Chem., 1994, *59*, 7682 and J. Med. Chem, 1996, *39* (11), 2219).

The 3-hydroxy-3-cyclobutene-1,2-dion-4-yl group (e.g. R.M.Soll, Bioorg. Med. Chem. Lett., 1993, *3* (4), 757 and W. A. Kinney, J. Med. Chem., 1992, 35 (25), 4720) can be prepared by the following sequence:- (1) a compound where R3 is $(CH_2)_nCHO$ (n = 0,1,2) is treated with triethylamine, carbontetrabromide triphenylphosphine to give initially $(CH_2)_nCH{=}CHBr$; (2) dehydrobromination of this intermediate to give the corresponding bromoethyne derivative $(CH_2)_nC{\equiv}CBr$ (for this 2 stage sequence see D. Grandjean et al, Tetrahedron Letters, 1994, *35* (21), 3529); (3) palladium-catalysed coupling of the bromoethyne with 4-(1-methylethoxy)-3-(tri-n-butylstannyl)cyclobut-3-ene-1,2-dione (Liebeskind et al, J. Org. Chem., 1990, *55*, 5359); (4) reduction of the ethyne moity to -CH2CH2- under standard conditions of hydrogen and palladium on charcol catalysis(see Howard et al, Tetrahedron, 1980, *36*, 171); and finally (4) acidic hydrolysis of the methylethoxyester to generate the corresponding 3-hydroxy-3-cyclobutene-1,2-dione group R.M.Soll, Bioorg. Med. Chem. Lett., 1993, *3* (4), 757).

The tetrazol-5-ylaminocarbonyl group may be prepared from the corresponding carboxylic acid and 2-aminotetrazole by dehydration with standard peptide coupling agents such as 1,1'-carbonyldiimidazole (P. L. Ornstein et al, J. Med Chem, 1996, *39* (11), 2232).

The alkyl- and alkenyl-sulphonylcarboxamides are similarly prepared from the corresponding carboxylic acid and the alkyl- or alkenyl-sulphonamide by dehydration with standard peptide coupling agents such as 1,1'-carbonyldiimidazole (P. L. Ornstein et al, J.Med.Chem., 1996, 39 (11), 2232).

The hydroxamic acid groups are prepared from the corresponding acids by standard amide coupling reactions eg N. R. Patel et al, Tetrahedron, 1987, *43* (22), 5375

2,4-Thiazolidinedione groups may prepared from the aldehydes by condensation with 2,4-thiazolidinedione and subsequent removal of the olefinic double bond by hydrogenation.

The preparation of 5-oxo-1,2,4-oxadiazoles from nitriles is decribed by Y.Kohara et al, Bioorg. Med. Chem. Lett., 1995, *5*(17), 1903.

1,2,4-Triazol-5-yl groups may be prepared from the corresponding nitrile by reaction with an alcohol under acid conditions followed by reaction with hydrazine and then an R^{10}-substituted activated carboxylic acid (see JB Polya in 'Comprehensive Heterocyclic Chemistry' Edition 1 p762, Ed AR Katritzky and CW Rees, Pergamon Press, Oxford 1984 and J.J. Ares et al, J. Heterocyclic Chem., 1991, 28(5), 1197).

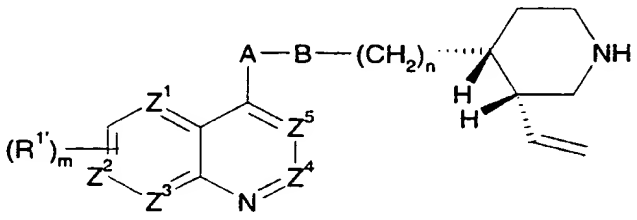
Other substituents on R^3 alkyl or alkenyl may be interconverted by conventional methods, for example hydroxy may be derivatised by esterification, acylation or etherification. Hydroxy groups may be converted to halogen, thiol, alkylthio, azido, alkylcarbonyl, amino, aminocarbonyl, oxo, alkylsulphonyl, alkenylsulphonyl or aminosulphonyl by conversion to a leaving group and substitution by the required group or oxidation as appropriate or reaction with an activated acid, isocyanate or alkoxyisocyanate. Primary and secondary hydroxy groups can be oxidised to an aldehyde or ketone respectively and alkyated with a suitable agent such as an organometallic reagent to give a secondary or tertiary alcohol as appropriate.

NH is converted to NR^4 by conventional means such as alkylation with an alkyl halide in the presence of base, acylation/reduction or reductive alkylation with an aldehyde.

It will be appreciated that under certain circumstances interconvertions may interfere, for example, A or B hydroxy groups and the piperidine NH will require protection e.g. as a carboxy- or silyl-ester group for hydroxy and as an acyl derivative for piperidine nitrogen, during conversion of $R^{1'}$, $R^{2'}$, $R^{3'}$ or $R^{4'}$, or during the coupling of the compounds of formulae (IV) and (V).

Examples containing a *trans*-3,4-substituted piperidine ring may be prepared from the trans-3-vinyl-4-substituted piperidine prepared from the corresponding 3-vinyl-4-*cis*-isomer by the method of G. Engler *et al.* Helv. Chim. Acta **68**, 789-800 (1985); also described in Patent Application EP 0031753 (Pharmindustrie).

The method involves heating a 3-vinyl-4-alkyl-piperidine derivative of formula (VIII):



(VIII)

(prepared as an intermediate in the process of the invention) in dilute acid, preferably hydrochloric acid at pH 3.5, with 0.3-1.0 mol equivalents of formaldehyde. The main product of the reaction is the *trans*-isomer, which may be separated from the small quantity of *cis* isomer present, by conventional silica gel chromatography. It is convenient to convert the mixture of cis- and *trans*-piperidines ($R^{4'}$ = H) to the tertiary amines of formula (I) by alkylation with an alkyl halide (preferably an iodide) in DMF in the presence of anhydrous potassium carbonate, prior to silica gel chromatography.

Compounds of formula (II) include quinine and derivatives thereof.

Compounds of formula (VI) are known compounds or may be prepared analogously, see for example Ihara et al JCS Perkin **1** 1988, 1277-1281.

Compounds of formulae (IV), (V) and (Vb) are known compounds, (see for example Smith *et al, J. Amer. Chem. Soc.*, 1946, 68, 1301) or prepared analogously, see for example the references cited above for reaction variant (a).

An isocyanate of formula (IV) may be prepared conventionally. A 4-amino derivative such as 4-amino-quinoline, and phosgene, or phosgene equivalent (eg triphosgene) provide the isocyanate or it may be prepared more conveniently from a 4-carboxylic acid by a 'one-pot' Curtius Reaction with diphenyl phosphoryl azide (DPPA) [see T. Shiori et al. *Chem. Pharm. Bull.* **35**, 2698-2704 (1987)].

The 4-carboxy derivatives are commercially available or may be prepared by conventional procedures for preparation of carboxy heteroaromatics well known to those skilled in the art. For example, quinazolines may be prepared by standard routes as described by T.A. Williamson in Heterocyclic Compounds, **6**, 324 (1957) Ed. R.C. Elderfield. Pyridazines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 3, Ed A.J. Boulton and A. McKillop

and napthyridines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 2, Ed A.J. Boulton and A. McKillop.

The 4-amino derivatives are commercially available or may be prepared by conventional procedures from a corresponding 4-chloro derivative by treatment with ammonia (O.G. Backeberg et. al., J. Chem Soc., 381, 1942.) or propylamine hydrochloride (R. Radinov et. al., Synthesis, 886, 1986).

A 4-chloroquinoline is prepared from the corresponding quinolin-4-one by reaction with phosphorus oxychloride ($POCl_3$) or phosphorus pentachloride, PCl_5. A 4-chloroquinazoline is prepared from the corresponding quinazolin-4-one by reaction with phosphorus oxychloride ($POCl_3$) or phosphorus pentachloride, PCl_5. A quinazolinone and quinazolines may be prepared by standard routes as described by T.A. Williamson in Heterocyclic Compounds, **6**, 324 (1957) Ed. R.C. Elderfield. Pyridazines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 3, Ed A.J. Boulton and A. McKillop and napthyridines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 2, Ed A.J. Boulton and A. McKillop.

4-Hydroxy-1,5-naphthyridines can be prepared from 3-aminopyridine derivatives by reaction with diethyl ethoxymethylene malonate to produce the 4-hydroxy-3-carboxylic acid ester derivative with subsequent hydrolysis to the acid, followed by thermal decarboxylation in quinoline (as for example described for 4-Hydroxy-[1,5]naphthyridine-3-carboxylic acid, Joe T. Adams *et al.*, *J.Amer.Chem.Soc.*, 1946, **68**, 1317). A 4-hydroxy-[1,5]naphthyridine can be converted to the 4-chloro derivative by heating in phosphorus oxychloride. A 4-amino 1,5-naphthyridine can be obtained from the 4-chloro derivative by reaction with n-propylamine in pyridine.
Similarly, 6-methoxy-1,5-naphthyridine derivatives can be prepared from 3-amino-6-methoxypyridine.

4-Methyl-1,5-naphthyridines can be prepared by methods well known to those skilled in the art (for example see H. Rapoport and A. D. Batcho, Journal of Organic Chemistry, 1963, 1753-1759). For example, nitrobenzene can be heated with oleum over a period of hours then water and a 3-aminopyridine added with heating. Slow addition of methyl vinyl ketone with heating produces the desired 4-methyl-1,5-naphthyridine.

1,5-Naphthyridines may be prepared by other methods well known to those skilled in the art (for examples see P.A. Lowe in "Comprehensive Heterocyclic Chemistry" Volume 2, p581-627, Ed A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984).

The 4-hydroxy and 4-amino-cinnolines may be prepared following methods well known to those skilled in the art [see A.R. Osborn and K. Schofield, *J. Chem. Soc.* 2100 (1955)]. For example, a 2-aminoacetopheneone is diazotised with sodium nitrite and acid to produce the 4-hydroxycinnoline with conversion to chloro and amino derivatives as described for 1,5-

naphthyridines. A 3-methyl substituent may be introduced by reaction of a 4-chlorocinnoline with lithium diisopropylamide at –75°C followed by alkylation with methyl iodide [see A. Turck et al. *Tetrahedron*, **47**, 13045 (1995)].

For compounds of formula (V) where Y is $NHR^{11'}$ suitable amines may be prepared from the corresponding acid or alcohol (Y is CO_2H or CH_2OH). In a first instance, an N-protected piperidine containing an acid bearing substituent, can undergo a Curtius rearrangement and the intermediate isocyanate can be converted to a carbamate by reaction with an alcohol. Conversion to the amine may be achieved by standard methods well known to those skilled in the art used for amine protecting group removal. For example, an acid substituted N-protectedpiperidine can undergo a Curtius rearrangement e.g. on treatment with diphenylphosphoryl azide and heating, and the intermediate isocyanate reacts in the presence of 2-trimethylsilylethanol to give the trimethylsilylethylcarbamate (T.L.Capson & C.D.Poulter, Tetrahedron Letters,1984, 25, 3515). This undergoes cleavage on treatment with tetrabutylammonium fluoride to give the 4-amine substituted N-protectedpiperidine. Alternatively, an acid group $(CH_2)_{n-1}CO_2H$ may be converted to $(CH_2)_nNHR_{11}$ by reaction with an activating agent such as isobutyl chloroformate followed by an amine $R^{11'}NH_2$ and the resulting amide reduced with a reducing agent such as $LiAlH_4$.

In a second instance, an N-protected piperidine containing an alcohol bearing substituent undergoes a Mitsunobu reaction (for example as reviewed in Mitsunobu, Synthesis, (1981), 1), for example with succinimide in the presence of diethyl azodicarboxylate and triphenylphosphine to give the phthalimidoethylpiperidine. Removal of the phthaloyl group, for example by treatment with methylhydrazine, gives the amine of formula (V).

Conversions of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ may be carried out on the intermediates of formulae (II), (IV), (V), (Vb) and (VI) prior to their reaction to produce compounds of formula (I) in the same way as described above for conversions after their reaction.

Where a *trans*-substituted compound of formula (I) is required, a *trans*-substituted piperidine moiety of formula (V) may be prepared from the corresponding *cis* isomer of formula (V) having an $R^{3'}$ vinyl group in the 3-position with a substituent that can subsequently be converted to the required group $(CH_2)_nY$, for example CH_2CO_2R (where R is an alkyl group eg methyl or ethyl), by heating in formaldehyde.

The pharmaceutical compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

The composition may be formulated for administration by any route, such as oral, topical or parenteral. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof is administered in the above-mentioned dosage range.

The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibiotics or with a β-lactamase inhibitor may be employed.

Compounds of formula (I) are active against a wide range of organisms including both Gram-negative and Gram-positive organisms.

The following examples illustrate the preparation of certain compounds of formula (I) and the activity of certain compounds of formula (I) against various bacterial organisms.

EXAMPLES

Example 1 [3R, 4R]-1-Heptyl-3-(1-(R or S)-hydroxy-2-cyanoethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

a) [3R,4R]-3-Ethenyl-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine.

A solution of quinine (497g) in acetic acid (460 ml) and water (3.8 l) was heated to reflux for 2 days. The mixture was basified with 40% aqeuous sodium hydroxide solution and extracted (2x) with dichloromethane. The organic extracts were washed with brine, dried (Na_2SO_4) and evaporated affording the title compound as a brown oil (497g,100%).

EI MH^+ 325, $C_{20}H_{24}N_2O$ requires 324.

b) [3R,4R]-3-Ethenyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

A solution of Example 1a(231.5g, 0.71 mol) in ethylene glycol (1.0l) was treated with hydrazine hydrate (50g, 1.0 mol) over 0.3 h. The mixture was warmed to 120°C for 1.5h. The mixture was then cooled to 10°C and potassium hydroxide (92.7g) was added and the mixture extracted with dichloromethane (2x). The dichloromethane extracts were washed with brine, dried (Na_2SO_4), and evaporated affording the title compound as a brown oil (217g, 100%).

EI MH^+ 311 $C_{20}H_{26}N_2O$ requires 310.

c) [3R,4R]-1-Benzyloxycarbonyl-3-ethenyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

A solution of crude Example 1b (496g, 1.5mol) in tetrahydrofuran (4.5 l) and water 3.3 l) was treated with solid potassium carbonate (219.6g, 1.6mol) and then a solution of benzyl chloroformate (258g, 1.5mol) in tetrahydrofuran (0.4 l) was added over 1 h. The mixture was stirred at room temperature for 15 h then sodium chloride (500g) and ethyl acetate (2.5 l) were added. After stirring for 0.25 h the organic phase was separated and the aqueous phase re-extracted with ethyl acetate. The combined ethyl acetate extracts were dried (Na_2SO_4) and evaporated affording as brown oil. This was chromatographed (in two portions) on 2.5kg silica Biotage cartridges eluting first with dichloromethene then 5% ethyl acetate in hexane to give the title compound a clear oil that crystallised on standing (450.5g, 67%).

EI MH^+ 445 $C_{28}H_{32}N_2O_3$ requires 444.

d) [3R,4R]-1-Benzyloxycarbonyl-3-(1-(R,S)-2-dihydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

A solution of Example 1c (215g, 0.48mol) in acetone (4.2 l) and water 0.53 l) under argon at 0°C was treated with osmium tetroxide (2.5g) in *t*-butanol (300 ml) dropwise over 0.5 h. A solution of N-methylmorpholine-N-oxide (77.6g, 0.66 mol) was in water (0.7 l) was then added dropwise over 1 h. The mixture was stirred for 16 h at room temperature. A solution of sodium metabisulphite (65.5g, 0.34 mol) in water (0.5 l) was added. After 4 h the mixture was filtered through celite (CAUTION – to remove Osmium metal), washing with acetone. The filtrate was concentrated by evaporation then solid sodium bicarbonate (50g) and ethyl acetate (2.5 l) were added. The organic extract was washed with brine dried (Na_2SO_4), and evaporated, giving a yellow oil (235g). This was purified by chromatography on a 2.5kg silica bioptage cartridge eluting with 1:1 ethyl acetate:hexane , neat ethyl acetate, then up to 5% methanol in ethyl acetate, affording the title compound as a yellow oil (179.9g, 78%).
EI MH^+ 478 $C_{28}H_{34}N_2O_5$ requires 477.

e) [3R, 4R]-1-Benzyloxycarbonyl-3-(2-(R, S)-oxiranyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

This was prepared by a modification of a related procedure by S. Takano *et al*, Synthesis, 1983, 116.

The above diol Example 1d (9.0g, 18.8 mmol) was dissolved in toluene (150ml) then triphenylphosphine (7.4g, 28.2 mmol) and diethylazodicarboxylate (4.9g, 28.2 mmol) were added. The mixture was heated to reflux under argon for 2.5 days. Evaporation and chromatography on silica eluting with a gradient of ethyl acetate/hexane (70/30) to neat ethyl acetate afforded a white solid (20.0g). Analysis of this material showed it to contain ca. 9g of the title compound, the balance being triphenylphosphine oxide.

E.I MH^+ 461 $C_{28}H_{32}N_2O_4$ requires 460

f) [3R, 4R]-1-Benzyloxycarbonyl-3-(1-(R,S)-hydroxy-2-cyanoethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

The above semi-purified epoxide Example 1e (10.9g, equivalent to approximately 5.0g, 10.9 mmol) was dissolved in tetrahydrofuran (160 ml) and treated with lithium cyanide in N,N-dimethylformamide (0.5 M;100ml, 50mmol). The mixture was heated to reflux under argon for 9 hours, and evaporated to dryness. The residue was partitioned between ethyl acetate and water. The organic extract was dried and evaporated affording the crude product as a brown solid (11g).

E.I. MH^+ 488, $C_{29}H_{33}N_3O_4$ requires 487.

g) [3R, 4R]-3-(1-(R, S)-hydroxy-2-cyanoethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

The above crude cyanohydrin Example 1f (approximately 10.9 mmol) was dissolved in ethanol (130ml) and hydrogenated over 10% palladium on charcol (5.6g) for 21 hours. Filtration and evaporation afforded a brown oil. Chromotagraphy on silica eluting with a mixture of aqueous ammonia:methanol:dichloromethane (1.5:15:30) afforded the pure product as an inseparable 2:1 mixture of diastereomers as a clear oil (1.28g, 33% over two stages from epoxide 1e)

E.I. MH^+ 354, $C_{21}H_{27}N_3O_2$ requires 353.

h) Title compounds

The above piperidine Example 1g (1.26g, 3.6 mmol) was dissolved in N,N-dimethylformamide (20ml), then treated with potassium carbonate (0.6g, 4.3 mmol) and heptyl iodide (0.65 ml, 0.9g, 3.9mmol). After 3.5 h the reaction mixture was evaporated and the residue partitioned between ethyl acetate and dilute brine. The organic extract was dried and evaporated giving a brown oil. Chromatography on silica eluting with aqueous ammonia-ethanol-dichloromethane (1.5-15-350) affording the individual diastereomers as yellow oil (combined yield 0.56g, 34%).

E.I. MH^+ 452, $C_{28}H_{41}N_3O_2$ requires 451.

Example 2. [3R, 4R]-1-Heptyl-3-(2-(R or S)-oxo-oxazolidin-5-yl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine

a) [3R, 4R]-1-Benzyloxycarbonyl-3-(1-(R,S)-hydroxy-2-azidoethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

This was prepared by the same procedure as for Example 1f, except that sodium azide was used instead of lithium cyanide and 0.5 equivalents of ammonium chloride were included in the reaction mixture.

E.I. MH^+ 504, $C_{28}H_{33}N_5O_4$ requires 503.

b) [3R, 4R]-1-Benzyloxycarbonyl-3-(1-(R,S)-hydroxy-2-aminoethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

The crude product Example 2a (2.58g, contaminated with $Ph_3P=O$) was dissolved in ethanol (70ml) and hydrogenated over 10% palladium on charcoal (0.9g) for 0.5h. This facilitated the selective reduction of the azide functionality in the presence of the N-benzyloxycarbonyl protecting group. Filtration and evaporation afforded the crude product as a pale yellow solid (2.3g).

E.I. MH^+ 478, $C_{28}H_{35}N_3O_4$ requires 477.

c) [3R, 4R]-1-Benzyloxycarbonyl-3-(1-(R,S)-hydroxy-2-benzyloxycarbonylaminoethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine

The above crude product (Example 2b) was dissolved in ethyl acetate and vigorously stirred with an equal volume of saturated aqueous sodium bicarbonate solution. Benzyl chloroformate (1.3 equivalents) was added and the mixture stirred under argon for 5 h. The phases were separated and the ethyl acetate extract dried and evaporated. The crude material was purified by chromatography eluting with an ethyl acetate/hexane gradient.

E.I. MH+ 612, C36H41N3O6 requires 611

d) [3R, 4R]-1-Benzyloxycarbonyl-3-(2-(R,S)-oxo-oxazolidin-5-yl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

The above alcohol (0.16g, 0.26mmol) was dissolved in a mixture of water:methanol:tetrahydrofuran (0.75ml:1.5ml:3ml) containing potassium hydroxide (0.32g). The mixture was stirred for 3h at room temperature then diluted with water (10ml) and extracted with ethyl acetate (30ml). The organic extract was dried ($Na_2 SO_4$) and evaporated. The crude material was purified by chromatography on silica eluting with a 0→2% ethanol in ethyl acetate gradient affording the product as a yellow oil (0.1g, 80%).

E.I. MH^+ 504, $C_{29}H_{33}N_3O_5$ requires 503.

e) [3R, 4R]-3-(2-(R,S)-oxo-oxazolidin-5-yl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine

Hydrogenation of the above compounds (Example 1d) according to the method for Example 1g with the variation that the reaction time was 4 h, gave the title compounds as an oil.

E.I. MH+ 370, C21H27N3O3 requires 369

f) Title compound

The title compounds were prepared by N-heptylation of the above compound (Example 2e) according to the method of Example 1h followed by chromatography on silica eluting with aqueous ammonia:ethanol:chloroform (1.5:15:400) to give the individual diastereomers (65mg and 24mg) as oils in a combined yield of 34%.

E.I. MH^+ 468, $C_{28}H_{41}N_3O_3$ requires 467.

Example 3. [3R, 4R]-1-Heptyl-3-(2-cyanoethyl)-4-[3-(6-methoxyquin lin-4-yl) propyl] piperidine.

a) [3R,4R]-1-Benzyloxycarbonyl-3-(2-hydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine.

The olefin Example 1c (10.00 g, 22.5 mmol) was dissolved in tetrahydrofuran (300 ml) and treated with with a solution of 9-borabicyclo(3.3.1.)nonane in hexane (0.5M, 135 ml, 67.6 mmol) and heated to reflux for 24h under argon. The cooled reaction mixture was treated with ethanol (70 ml) and 2M aqueous sodium hydroxide solution (70 ml), then 27.5 w/v aqueous hydrogen peroxide solution (45 ml) was added over 20 minutes.After 1h ethyl acetate and water were added, and the organic extract dried and evaporated. The crude product was purified by chromatography on silica gel eluting with an ethyl acetate gradient affording the titile product as a yellow oil (6.3g, 60%).
E.I. MH^+ 463, $C_{28}H_{34}N_2O_4$ requires 462.

b) (3R, 4R)-3-(2-hydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

This was prepared in approximately quantitative yield from the above N-benzyloxycarbonyl piperidine (Example 3a) by hydrogenation according to the procedure for Example 1g, with the variation that the reaction time was 3h.
E.I. MH^+ 329, $C_{20}H_{28}N_2O_2$ requires 328.

c) (3R, 4R)-1-*t*-butyloxycarbonyl-3-(2-hydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

Example 3b was dissolved in dichloromethane-N,N-dimethylformamide and treated with triethylamine (1.2 eq),di-*t*-butylcarbonic anhydride (1.1 equivalents) and N,N-dimethylaminopyridine (catalytic quantity). After stirring overnight the mixture was evaporated and purified by chromatography on silica eluting with a gradient of ethyl acetate/hexane, giving the product as an oil (3.8g, 34%)
E.I MH+ 429, 329 (loss of $CO_2C_4H_9$), $C_{25}H_{36}N_2O_4$ requires 428.

d) (3R, 4R)-1- *tert*-butyloxycarbonyl-3-[2-(4-methylphenyl)sulfonyloxyethyl]-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

Example 3c (2.2g, 5.1 mmol) was dissolved in dichloromethane (50ml), then triethylamine (0.85ml, 0.62g, 6.1 mmol), N,N-dimethylaminopyridine (catalytic) and 4-methylphenylsulfonyl chloride (1.1g, 5.6 mmol) were added. After 20h the mixture was diluted with more dichloromethane and washed with water. The organic extract was dried (Na_2SO_4) and evaporated.

Chromatography on silica eluting with ethyl acetate:hexane (1:1) afforded the product as a yellow oil (1.8g, 61%).
E.I. MH+ 583, $C_{32}H_{42}N_2O_6S$ requires 582.

e) (3R, 4R)-1- *t*-butoxycarbonyl-3-(2-cyanoethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

Example 3d (1.8g, 31mmol) was dissolved in N,N-dimethylformamide (15ml) and treated with sodium cyanide (0.3g, 6.2 mmol). The mixture was stirred at room temperature for 16 h then at 40° for 1h. The mixture was evaporated to dryness and the residue was partitioned between ethyl acetate and water. The organic extract was dried ($MgSO_4$) and evaporated to give the product as an oil, (67%).
E.I. MH+ 438, $C_{26}H_{35}N_3O_3$ requires 437.

f) (3R, 4R)-3-(2-cyanoethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

Example 3e (0.9g) was treated with 1:1 trifluoroacetic acid:dichloromethane (25 ml)at 0 C. After 1h the reaction mixture was evaporated and the residue partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution.. The organic extract was dried and evaporated to give the title compound as an oil in approximately quantitative yield.
E.I MH+ 338, $C_{21}H_{27}N_2O_2$ requires 337.

g) Title compound

The title compound was prepared from Example 3f by heptylation using the procedure of Example 1h, giving the purified product as an oil
(0.55g, 62%)
E.I. MH^+ 436, $C_{28}H_{14}N_3O$ requires 435.

Example 4. [3R, 4R]-1-Heptyl-3-(3-carboxyethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

Hydrolysis of the corresponding cyanoethyl compound (Example 3g) (0.35g,0.8mmol) with concentrated hydrochloric acid and dioxane (9ml of each) at reflux for 11h followed by evaporation and chromatography on silica (eluting with 1.5:15:50 aqueous ammonia:methanol:chloroform) afforded the title compound (0.23g, 55%) as an oil.
E.I. MH^+, 455, $C_{28}H_{42}N_2O_2$ requires 454.

Example 5. [3R, 4R]-1-Heptyl-3-carboxy–4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

a) (3R, 4R)-3-(1-(R,S)-2-Dihydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine

The title compounds (4.7g) were prepared in approximately quantitative yield by hydrogenation of Example 1d according to the same procedure as for Example 1g, with the variation the reaction time was 3h.

E.I. MH+ 345, $C_{20}H_{28}N_2O_3$ requires 344.

b) (3R, 4R)-3-(1-(R,S)-2-Dihydroxyethyl)-1-heptyl-4-[3-(6-methoxyquinolin-4-yl) propyl]piperidine

The title compounds were prepared in approximately 60% yield by alkylation at room temperature with heptyl iodide (1.1 equivalents) in N,N-dimethylformamide as solvent and potassium carbonate (1.2 equivalents) as base, following an analogous procedure to Example 1h.

E.I. MH+ 443, $C_{27}H_{42}N_2O_3$ requires 442.

c) Title compounds

A solution of the above diol (Example 5b) (0.4g) in acetone (10ml) was treated at 0°C with Jones reagent (~50 drops). After 2h the reaction mixture was neutralised with saturated aqueous sodium bicarbonate solution and extracted (3x) with ethyl acetate. The combined organic extracts were dried and evaporated. Chromatography on silica eluting with aqueous ammonia-ethanol-chloroform (1.5:15:300) afforded the title compounds as a yellow oil (32 mg, 8%).

E.I. MH^+ 427, $C_{26}H_{38}N_2O_3$ requires 426.

Example 6. [3R, 4R]-1-Heptyl-3-(carboxymethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine.

a) [3R,4R]-3-Ethenyl-1-heptyl-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

This was prepared in 66% yield from (Example 1b) by heptylation according to the procedure for Example 1h.

E.I MH+ 409, $C_{27}H_{40}N_2O$ requires 408.

b) (3R, 4R)-1-heptyl-3-(2-hydroxyethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine

This was prepared from Example 6a in 40% yield by the same hydroboration/oxidation procedure as for Example 3a.

E.I MH+ 427, $C_{27}H_{42}N_2O_2$ requires 426.

c) (3R, 4R)-1-heptyl-3-(2-carboxymethyl)-4-[3-(6-methoxyquinolin-4-yl) propyl] piperidine

This was prepared in 15% yield from Example 6b using the same oxidation procedure as for Example 5c.
E.I. M^+H 441, $C_{27}H_{40}N_2O_3$ requires 440.

Example 7 [3R, 4R]-1-Heptyl-3-(1-(R or S)-hydroxy-2-carboxyethyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

A solution of Example 1(60 mg, 0.13 mmol) in concentrated hydrochloric acid:dioxane (6 ml:3 ml) was heated to reflux for 4h. The mixture was neutralised with saturated aqueous sodium bicarbonate solution and extracted (3X) with ethyl acetate. The combined organic extracts were dried and evaporated and the crude product chromatographed on silica eluting with aqueous ammonia:methanol:chloroform (1.5:15:50) giving the title compounds as a colourless oil,
(0.019g, 30%).
E.I. MH+ 471, $C_{28}H_{42}N_2O_3$ requires 470.

Example 8 [3R, 4R]-1-Heptyl-3-(2-(*E*-)-carboxyethenyl)-4-[3-(6-methoxyquinolin-4-yl)propyl]piperidine

A solution of Example 1(48 mg, 0.11 mmol) in concentrated hydrochloric acid:dioxane (5 ml:3 ml) was heated to reflux for 24h. The mixture was neutralised with saturated aqueous sodium bicarbonate solution and extracted (3X) with ethyl acetate. The combined organic extracts were dried and evaporated and the crude product chromatographed on silica eluting with aqueous ammonia:methano:chloroform (1.5:15:50) giving the title compound as a colourless oil, (0.015g, 31%).
E.I. MH+ 453, $C_{28}H_{40}N_2O_2$ requires 452.

Example 9. N-(cis-3-(R/S)-Ethoxycarbonyl–1-heptyl-4-(S/R)-piperidyl)-N'-(6-methoxyquinolin-4-yl)urea oxalate

a) 4-Benzylamino-1-tert-butoxycarbonyl-3-ethoxycarbonyl-1,2,5,6-tetrahydropyridine

A solution of 1-tert-butoxycarbonyl-3-ethoxycarbonylpiperidin-4-one (prepared from 3-ethoxycarbonylpiperidin-4-one and di-tert-butyl-dicarbonate in dichloromethane and triethylamine) (25g) and benzylamine (10.85g) in toluene was heated under reflux in a Dean and Stark apparatus for 18 hours and then evaporated to dryness to give an oil.

b) cis- 4-(S/R)-Benzylamino-1-tert-butoxycarbonyl-3-(R/S)-ethoxycarbonylpiperidine

The enamine (9a) (25g) in ethanol (300ml) was hydrogenated over platinum oxide (1.5g) for 4 days, filtered, and evaporated to dryness. It was chromatographed on silica gel (ethyl acetate-hexane) to afford the title compound as an oil.

MS (+ve ion electrospray) m/z 363 (MH+).

c) cis-4-(S/R)-Amino-1-tert-butoxycarbonyl-3-(R/S)-ethoxycarbonylpiperidine

The amine (9b) (4g) in ethanol (80ml) containing acetic acid (0.73g) was hydrogenated at 50psi (Parr reaction vessel) over 10% palladium-carbon (1g) for 18 hours, filtered and evaporated to dryness to afford the acetate salt of the title compound as a white solid (3g).

MS (+ve ion electrospray) m/z 273 (MH+).

It was converted to the oily free base by extraction using dichloromethane-sodium carbonate and drying over sodium sulfate.

d) N-(cis-1-tert-Butoxycarbonyl-3-(R/S)-ethoxycarbonyl-4-(S/R)-piperidyl)-N'-(6-methoxyquinolin-4-yl)urea

A suspension of 6-methoxyquinoline-4-carboxylic acid (0.98g) in dry toluene (50ml) was treated with triethylamine (1.95g) followed by diphenylphosphoryl azide (1.39g) and the mixture was stirred at room temperature for 8 hours. The resultant solution was treated with the amine (9c) and then heated under reflux for 4 hours and evaporated to dryness. The product was chromatographed on silica gel (ethyl acetate-hexane) to afford the title compound (1.98g) as a foam.

MS (+ve ion electrospray) m/z 473 (MH+).

e) N-(cis-3-(R/S)-Ethoxycarbonyl-4-(S/R)-piperidyl)-N'-(6-methoxyquinolin-4-yl)urea

The urea (9d) (1.0g) was treated with dichloromethane (30ml) and trifluoroacetic acid (20ml) at room temperature for 3 hours and evaporated to dryness. It was basified with sodium carbonate solution and evaporated to dryness. The solid was extracted three times with ethanol-chloroform (1:9) and evaporated to dryness to afford a foam (0.75g).

MS (+ve ion electrospray) m/z 373 (MH+).

f) Title compound

The amine (9e) (0.75g) in dry ethanol (15ml) was treated with heptaldehyde (0.636g) and sodium triacetoxyborohydride (0.459g) for 1 hour at room temperature. Sodium bicarbonate solution was added and the mixture was extracted with dichloromethane, dried over sodium sulfate, and evaporated to afford an oil.

Chromatography on silica gel (ethyl acetate-hexane) gave the title compound (0.68g) as an oil.

MS (+ve ion electrospray) m/z 471 (MH+).

The free base in dichloromethane was treated with 1 molar equivalent of oxalic acid in ether and the resulting solid was collected, triturated with ether, to afford the oxalate salt as a white solid.

Example 10. N-(cis-3-(R/S)-Ethoxycarbonyl-1-heptyl-4-(S/R)-piperidyl)-N'-(6-methoxy-[1,5]-naphthyridin-4-yl)urea oxalate

a) 4-Hydroxy-6-methoxy-[1,5]naphthyridine-3-carboxylic acid ethyl ester

3-Amino-6-methoxypyridine (12.41 g) and diethyl ethoxymethylene malonate (20.2 ml) in Dowtherm A (400 ml) were heated at reflux, under argon for 1 hour. The cooled reaction mixture was poured into pentane (1 litre). The precipitated solid was collected by filtration, washed with pentane and dried to afforded a solid (24.78 g, crude).

b) 4-Hydroxy-6-methoxy-[1,5]naphthyridine-3-carboxylic acid

The ester (10a) (0.642g) in 10% aqueous sodium hydroxide (115 ml) was heated at reflux for 1.5 hours. The reaction mixture was cooled then acidified with glacial acetic acid. The precipitated solid was collected by filtration, washed with water and dried *in vacuo* to afford a beige solid (0.542g).

MS (+ve ion electrospray) m/z 221 (MH^+).

c) 4-Chloro-6-methoxy-[1,5]naphthyridine

The acid (10b) (6.82 g) was heated in quinoline (20ml) at reflux for 2 hours, the mixture was cooled and poured into ether (200ml) and the orange solid was filtered and washed with ether (5 x 200ml). A sample (3.87g) of the dried solid was treated with phosphorus oxychloride (30ml) at room temp for 3 hours, the solvent was removed *in vacuo* and the residue quenched with crushed ice (200g). The mixture was basified with ammonia solution and filtered. The solid was washed with dichloromethane (10 x 100ml), which was evaporated and chromatographed on silica gel (dichloromethane as eluent) to give a yellow solid (3.0g).

MS (+ve ion electrospray) m/z 195, 197 (MH^+).

d) 4-Amino-6-methoxy-[1,5]naphthyridine

A solution of the chloro compound (10c) (2.0g) in pyridine (30ml) was treated with n-propylamine hydrochloride (6.0g) and the mixture heated at reflux for 16 hours. The reaction mixture was cooled and partitioned between water and ethyl acetate. The

aqueous phase was washed with ethyl acetate, the combined organics dried (Na_2SO_4) and the solvent removed under reduced pressure. Purification by chromatography on silica gel (5-10% methanol in dichloromethane) afforded a yellow solid (1.0g).
^1H NMR ($CDCl_3$) δ: 4.05 (3H, s), 5.36 (2H, bs), 6.71 (1H, d, J=5 Hz), 7.08 (1H, d, J=9Hz), 8.10 (1H, d, J=9Hz), 8.40 (1H, d, J=5Hz).
MS (+ve ion electrospray) m/z: 176 (MH^+).

e) N-(cis-1-tert-Butoxycarbonyl-3-(R/S)-ethoxycarbonyl-4-(S/R)-piperidyl)-N'-(6-methoxy-[1,5]-naphthyridin-4-yl)urea

To a solution of amine (10d) (0.5g) in chloroform (4ml) was added 1,1'-carbonyldiimidazole (0.76g) and dimethylaminopyridine (0.38g) and the solution was stirred at room temperature for 3.5 hours and evaporated to dryness. The product was heated at 100°C in dry DMF (7ml) containing the amine (9c) (0.85g), for 3 hours. Aqueous sodium carbonate was added and the mixture was extracted with dichloromethane, dried over sodium sulfate, and evaporated to afford a foam. Chromatography on silica gel (ethyl acetate-hexane) gave an oil (0.928g).
MS (+ve ion electrospray) m/z 474 (MH+).

f) N-(cis-3-(R/S)-Ethoxycarbonyl-4-(S/R)-piperidyl)-N'-(6-methoxy-[1,5]-naphthyridine-4-yl)urea

The urea (10e) (0.92g) was treated with dichloromethane (20ml) and trifluoroacetic acid (30ml) at room temperature for 3 hours and evaporated to dryness. It was basified with sodium carbonate solution and evaporated to dryness. The solid was extracted three times with warm ethanol-chloroform (1:9) and evaporated to dryness to afford a foam (0.80g).
MS (+ve ion electrospray) m/z 374 (MH+).

g) Title compound

The amine (10f) (0.80g) in dry ethanol (20ml) was treated with heptaldehyde (0.26g) and sodium triacetoxyborohydride (0.82g) for 1 hour at room temperature. Sodium bicarbonate solution was added and the mixture was extracted with dichloromethane, dried over sodium sulfate, and evaporated to afford an oil. Chromatography on silica gel (ethyl acetate-hexane) gave the title compound (0.72g) as an oil.
MS (+ve ion electrospray) m/z 472 (MH+).

The free base in dichloromethane was treated with 1 molar equivalent of oxalic acid in ether and the resulting solid was collected, triturated with ether, to afford the oxalate salt as a white solid.

Example 11. N-(cis-3-(R/S)-Aminocarbonyl–1-heptyl-4-(S/R)-piperidyl)-N'-(6-methoxy-[1,5]-naphthyridin-4-yl)urea oxalate

The ester Example 10 (0.105g) in methanol (2ml) was heated with ammonia (3ml) and sodium cyanide (2mg) at 50°C (sealed bomb) for 3 days and evaporated to dryness. Chromatography on silica gel (ethyl acetate then methanol-dichloromethane) gave the title compound (0.024g), as the free base.
MS (+ve ion electrospray) m/z 443 (MH+).
The free base in dichloromethane-ether was converted to the oxalate salt in the normal manner, affording a white solid.

Example 12. [3R, 4R]-1-Heptyl-4-[3-(R/S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]-3-(2-(R or S)-oxo-oxazolidin-5-yl)-piperidine

a) 9-O-Acetyl-(R/S)-10,11-epoxyquinine

A solution of Example 13b (57g, 140 mmol) in toluene (1 l) was treated with triphenyl phosphine (114g, 440 mmol) and diethylazodicarboxylate (80 ml, 510 mmol). The mixture was heated to reflux for 8h, the cooled and chromatographed eluting with methanol in dichloromethane to give the product as an oil (12g, 22%).
^{1}H NMR ($CDCl_3$) δ: 4.00 (3H, s), 6.50 (1H, m), 7.20-7.50 (3H, m), 8.03 (1H, d), 8.72 (1H, d). EI MH^+ 383 $C_{22}H_{26}N_2O_4$ requires 382.

b) 9-O-Acetyl-(R/S)-11-azido-10-hydroxy-10,11-dihydoquinine

A solution of Example 12a (12g, 31.4 mmol) in N,N-dimethylformamide (100 ml) was treated with sodium azide (11.7g) and ammonium chloride (1g) and heated at 140° C for 7h. The mixture was evaporated and the residue partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic extract was dried and evaporated. The residue was chromatographed on silica eluting with methanol in dichloromethan affording the title compound as an orange foam (2.03g, 15%).
^{1}H NMR ($CDCl_3$) δ: 3.95 (3H, s), 6.50 (1H, m), 7.30-7.50 (3H, m), 8.00 (1H, d), 8.70 (1H, d). EI MH^+ 426 $C_{22}H_{27}N_5O_4$ requires 425

c) 9-O-Acetyl-11-amino-10-hydroxy-10,11-dihydroquinine

Azide 12b (2.03 g, 4.8 mmol) in ethanol (30 ml) was hydrogenated over 10% palladium on charcoal for 2 hours. The mixture was filtered through celite and

evaporated. Chromatography on silica gel eluting with 5-20% methanol in dichloromethane containing 0.5-2% ammonia gave an orange oil (0.87g,46%). ^{1}H NMR ($CDCl_3$) δ: 3.96 (3H,s), 6.50 (1H,d), 7.32-7.48 (3H,m), 8.02 (1H, d), 8.74 (1H,d), E.I. MH^+ 400, $C_{22}H_{29}N_3O_4$ requires 399.

d) 5-(R/S)-{2-S-[R-acetoxy-(6-methoxyquinolin-4-yl)methyl]-5-R-quinuclidinyl}oxazolidin-2-one

A solution of amine 12c (0.65 g, 1.63 mmol), in dichloromethane (25 ml) was treated with triethylamine (0.56 ml, 4.0 mmol) and triphosgene (0.20 g, 0.67 mmol). After being stirred for 2 hours, further triphosgene (0.05 g, 0.16 mmol) was added and stirring continued for 1 hour. The mixture was diluted with dichloromethane and washed with sodium carbonate solution, dried and evaporated. Chromatography on silica gel eluting with 2-5% methanol in dichloromethane gave an off-white foam (0.54g, 66%), ^{1}H NMR ($CDCl_3$) δ: 3.96 (3H,s), 4.45(1H,m), 5.43 (1H,s), 6.47 (1H,d), 7.30-7.45 (3H,m), 8.02 (1H,d), 8.74 (1H,d). E.I. MH^+ 426, $C_{23}H_{27}N_3O_5$ requires 425.

e) (3R,4R)-3-(2-Oxo-oxazolidin-5-yl)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine

A solution of 12(d) (0.266 g, 0.63 mmol) in water/acetic acid (3 ml/0.3 ml) was heated to reflux for 2 days. The mixture was basified with 40% sodium hydroxide solution and extracted with ethyl acetate. The organic extracts were dried and evaporated to give the title compound as a yellow oil (105 mg), ^{1}H NMR ($CDCl_3$) δ: 3.94 (3H,s), 4.85(1H,m), 5.10 (1H,bs), 7.40 (1H,dd), 7.70 (1H, d), 7.85 (1H, d), 8.05 (1H,d), 8.90 (1H,d), E.I. MH^+ 384 $C_{21}H_{25}N_3O_4$ requires 383.

f) (3R,4R)-1-Heptyl-3-(2-oxo-oxazolidin-5-yl)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine

A solution of Example 12e(105 mg) in N,N-dimethylformamide (3 ml) was treated with potassium carbonate (0.14g) and heptyl iodide (0.2 ml). After 2h the reaction mixture was diluted with ethyl acetate and washed with sodium carbonate solution, brine, dried and evaporated. Chromatography on silica eluting with methanol in dichloromethane gave the title compound as a clear oil (70 mg, 23% over 2 stages), ^{1}H NMR ($CDCl_3$) δ: 0.85 (3H, t), 1.20-1.45 (10H, m), 3.94 (3H,s), 4.85(1H,m), 5.65 (1H,bs), 7.40 (1H,dd), 7.75 (1H, d), 7.90 (1H, d), 8.10 (1H,d), 8.90 (1H,d), E.I. MH^+ 482 $C_{28}H_{39}N_3O_4$ requires 481.

g) Title compounds

A solution of Example 12f (42 mg, 0.09 mmol) in 2-propanol (5 ml) wastreated with sodium borohydride (20 mg). After 2h the mixture was diluted with water and extracted with dichloromethane. The organic extract was dried and evaporated. Chromatography on silica eluting with methanol in dichloromethan afforded the title compounds as a clear oil (30 mg, 71%),
^{1}H NMR ($CDCl_3$) δ: 0.85 (3H, t), 1.20-1.45 (10H, m), 3.95 (3H,s), 4.85(1H,m), 5.90 (1H,m), 5.90 (1H, s), 7.25 (1H,dd), 7.32 (1H, d), 7.55 (1H, dd), 8.00 (1H,d), 8.70 (1H,m), E.I. MH^+ 484 $C_{28}H_{41}N_3O_4$ requires 483.

Example 13. [3R, 4R]-1-Heptyl-3-cyanomethyl-4-[3-(R/S)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine

a) O-Acetylquinine

A solution of quinine (97.2g , 300 mmol) in pyridine (300 ml) was treated with acetic anhydride (31 ml, 34g, 333mmol). After 4h the mixture was evaporated to dryness, azeotroping with water then toluene, affording the product an an oil which was used without further purification.
EI MH^+ 367, $C_{22}H_{26}N_2O_3$ requires 366

b) 9-O-Acetyl-10,11-dihydro-(R,S)10,11-dihydroxyquinine

A solution of Example 13a in acetone-water (400 ml-150 ml) was treated with osmium tetroxide (2g) in *tert*-butanol (50 ml). A solution of N-methylmorpholine N-oxide (49.1g, 420 mmol) was added. After 2 days more osmium tetroxide (1g) was added. After a further day sodium metabisulphite (30g) in water (100 ml) was added. After 2h the mixture was filtered and evaporated. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic extract was dried and chromatographed to give the diols as a white foam (109g, 91% over two steps).
EI MH^+ 401, $C_{22}H_{28}N_2O_5$ requires 400

c) 9-O-Acetyl-10-al-11-norquinine

A solution of Example 13b (1.8g, 4.4 mmol) in pH7 phosphate buffer (30 ml) was treated at 0° C with a slurry of sodium periodate (1.9g, 8.8 mmol) in water (10 ml). After 0.5h, the mixture was extracted three times with chloroform. The chloroform extract was dried and evaporated to give the title compound as a white foam (1.1g, 65%).
^{1}H NMR ($CDCl_3$) δ: 3.95 (3H, s), 6.45 (1H, d), 7.35 (1H, m), 7.40 (1H, m), 8.05 (1H, d), 8.75 (1H, d), 9.75 (1H,s). EI MH^+ 367, $C_{21}H_{24}N_2O_4$ requires 368

d) 10-Cyano-10,11-dihydro-11-norquinine

To a stirred suspension of potassium t-butoxide (6.28 g) in 1,2-dimethoxyethane (23 ml) kept below –30°C was added dropwise a solution of tosylmethyl isocyanide (5.62 g) in 1,2-dimethoxyethane (23 ml). After stirring for 20 minutes, a solution of Example 13c (10g) in 1,2-dimethoxyethane (32 ml) and THF (30 ml) was slowly added to the reaction mixture at –50 to –60 °C. After 50 minutes methanol (40ml) was added to the cold solution which was heated at reflux for 15 minutes. The solvent was removed under reduced pressure and saturated sodium bicarbonate solution added. The mixture was extracted with dichloromethane, washed with brine, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. Chromatogrphy on silica gel eluting with 5% methanol in dichloromethane gave a yellow foam (3.58g, 39 %).

^{1}H NMR ($CDCl_3$) δ: 8.70 (d,1H), 8.00 (d,1H), 7.54 (d, 1H), 7.34 (d,1H) 7.19 (d, 1H) 5.62 (s,1H), 3.88 (s,3H) 3.45-3.6 (m,1H), 3.15-3.25 (m,1H), 3.00-3.15 (m,1H), 2.55-3.25 (m, 1H), 2.38-2.50 (m, 1H), 2.18-2.25 (m, 2H), 2.10-1.80 (m, 4H), 1.35-1.6 (m, 2H). EI MH^+ 338 $C_{20}H_{23}N_3O_2$ requires 337.

e) [3R,4R]-3-Cyanomethyl-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine

A solution of Example 13d (3.58 g) in glacial acetic acid (4 ml) and water (40 ml) was heated at reflux under a flow of argon for 36 hours. The reaction mixture was taken to pH12 with sodium hydroxide solution. The mixture was extracted into ethyl acetate, dried over anyhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. Chromatography on silica gel eluting with 5 to 10 % methanol in dichloromethane gave the compound as an oil (0.830 g, 23%).

^{1}H NMR ($CDCl_3$) δ: 8.89 (d, 1H), 8.07 (d, 1H), 7.85 (d,1H), 7.61 (d,1H), 7.41 (d, 1H), 3.95 (s,3H), 3.20-3.01 (m,4 H), 2.83-2.58 (m,3 H), 2.43-2.34 (m,1H), 2.00-2.18 (m,1H), 1.85-1.70 (m,3H), 1.65-1.50 (m,1H), 1.45-1.25 (m,1H).

EI MH^+ 338 $C_{20}H_{23}N_3O_2$ requires 337.

f) [3R,4R]-1-Heptyl-3-cyanomethyl-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine

Amine 13e (0.830g) was heptylated according to the method for example 1h to give the compound as an oil (0.856g, 80%).

^{1}H NMR ($CDCl_3$) δ: 8.89 (d,1H), 8.07 (d,1H), 7.85 (d,1H), 7.61 (d,1H), 7.41 (d, 1H), 3.96 (s,3H), 3.15-2.96 (m,3H), 2.88-2.70 (m,2H), 2.45-1.90 (m,6H), 1.80-1.20 (m, 15H), 0.89 (t, 3H)

EI MH^+ 436 $C_{27}H_{37}N_3O_2$ requires 435.

g) Title compound

A solution of ketone 13f (0.738g) in isopropanol (10 ml) was treated at 0°C with sodium borohydride (0.064g). The mixture allowed to warm to room temperature. After 3 hours, water (20 ml) was added and the mixture extracted with ethyl acetate. The combined organic layers were dried over anyhdrous magnesium sulphate, filtered and the solvet removed under reduced pressure. Chromatography on silica gel eluting with 1 to 5 % methanol in dichloromethane gave the title compound as a yellow oil (0.595 g, 80 %). ^{1}H NMR ($CDCl_3$) δ: 8.75 (d,1H), 8.05 (d,1H), 7.50 (d,1H), 7.37 (d,1H), 7.25 (d, 1H), 5.40 (m,1H), 3.94 (s,3H), 3.05-2.55 (m,3H), 2.45-2.15 (m,3H), 2,10-1.75 (m,5H), 1.75-1.10 (m,15H), 0.88 (t,3H). EI MH^+ 438 $C_{27}H_{39}N_3O_2$ requires 437.

Example 14. [3R, 4R]-1-Heptyl-3-cyanomethyl-4-(2-(R)-hydroxy-3-(6-methoxyquinolin-4-yl)propyl]piperidine

a) [3R,4R]-1-Heptyl-3-cyanomethyl-4-[2(R),3(R)-oxiranyl-3-(6-methoxyquinolin-4-yl)propyl]piperidine

A solution of 13d (3.2 g) in toluene (30 ml) and N,N-dimethylformamide (3ml) was heated at 80°C with heptyl bromide(1.65ml) overnight under a stream of argon. Starting material was still present so heptyl iodide (0.8 ml) was added and the mixture heated at 80°C for 2 hours. The solvent was removed under reduced pressure and the residue was dissolved in *t*-butanol (40ml) and THF (10 ml). Potassium t-butoxide (1M in THF, 11ml) was added and the mixture heated at reflux under a stream of argon for 1 hour. The mixture was allowed to cool to room temperature, silica added and the solvent removed under reduced pressure. Chromatography on silica gel (dry loaded) eluting with 1 to 5 % methanol in dichloromethane gave the compound as a brown oil (1.72 g, 42%). ^{1}H NMR ($CDCl_3$) δ: 8.75 (d,1H), 8.07 (d,1H), 7.43 (d,1H), 7.27 (m,2H), 4.18 (s,1H), 3.95 (s,1H), 3.05-2.65 (m,4H), 2.40-1.15 (m,23H), 0.90 (t,3H)
EI MH^+ 436 $C_{27}H_{37}N_3O_2$ requires 435.

b) Title compound

A solution of oxirane 14a (1.32 g) in ethanol (30 ml), was treated with10% palladium on charcoal (0.85 g) and the mixture hydrogenated at atmospheric pressure for 4 hours. The mixture was filtered through a small plug of celite and the solvent removed under reduced pressure. Chromatography on silica gel eluting with 2% methanol in dichloromethane gave the target compound as a brown oil (0.462 g, 35 %).
^{1}H NMR ($CDCl_3$) δ: 8.37 (d,1H), 7.84 (d,1H), 7.28 (m,2H), 7.15 (d,1H), 4.24 (m,1H), 3.95 (s,3H), 3.20-3.30 (m,1H), 3.10-2.60 (m,5H), 2.45-1.10 (m,21H), 0.86 (t,3H).
EI MH^+ 438 $C_{27}H_{39}N_3O_2$ requires 437.

The following compound Examples were prepared following the procedures described in the synthetic methodology section and previous preparative Examples:

Example 15. N-(cis-3-(R/S)-Carboxy-1-heptyl-4-(S/R)-piperidyl)-N'-(6-methoxyquinolin-4-yl)urea tris-trifluoroacetate

MS (+ve ion electrospray) m/z 443 (MH+).

Example 16. cis-3-(R/S)-Ethoxycarbonyl-1-heptyl-4-(S/R)-(6-methoxyquinolin-4-yl)aminocarbonyloxypiperidine

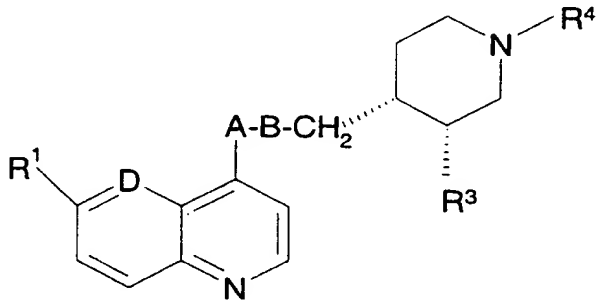
MS (+ve ion electrospray) m/z 472 (MH+).

Example 17. cis-3-(R/S)-Carboxy-1-heptyl-4-(S/R)-(6-methoxyquinolin-4-yl)aminocarbonyloxypiperidine

MS (+ve ion electrospray) m/z 444 (MH+).

The following compounds were prepared following the procedures described in the synthetic methodology section and previous preparative Examples

TABLE 1



Example	A-B	n	R^1	D	R_3	R_4
18	CH_2CH_2	1	CH_3O	C	CH_2CN	n-heptyl
19	$CH(NH_2)CH_2$	1	CH_3O	C	CH_2CN	n-heptyl
20	CH_2CH_2	1	CH_3O	C	CH_2COOH	5-methylhexyl
21	$CH(N_3)CH_2$	1	CH_3O	C	CH_2CN	n-heptyl
22	CH_2CH_2	1	CH_3O	C	$CONH_2$	n-heptyl
23	CH_2CH_2	1	CH_3O	C	CH_2COOH	n-hexyl
24	$CO.CH_2$	1	CH_3O	C	CH_2CN	n-heptyl
25	CH_2CH_2	1	CH_3O	C	$CH_2CH(CH_3)COOH$	n-heptyl
26	CH_2CH_2	1	CH_3O	C	CH_2COOH	cinnamyl
27	CH_2CH_2	1	CH_3O	C	CH_2COOH	3-phenylpropyl
28	CH(OH)CH2	1	CH_3O	C	CH_2COOH	n-heptyl
29	$CH(NH_2)CH_2$	1	CH_3O	C	CH_2COOH	n-heptyl
30	$CH(OH)CH_2$	1	CH_3O	C	CH(OH)COOH	n-heptyl
31	$CO.CH_2$	1	CH_3O	C	CH(OH)COOH	n-heptyl
32	$CH_2CH(OH)$	1	CH_3O	C	CH_2COOH	n-heptyl
33	NHCO	1	CH_3O	N	CH_2COOH	n-heptyl
34	CH_2CH_2	1	OH	C	CH_2COOH	n-heptyl
35	NHCOO	0	CH_3O	C	$CONH_2$	n-heptyl
36	oxirane	1	CH_3O	C	CH_2CN	n-heptyl

Biological Activity

The MIC (μg/ml) of test compounds against various organisms was determined: S. aureus Oxford, S. aureus WCUH29, S. aureus Carter 37, E. faecalis I, M. catarrhalis Ravasio, S. pneumoniae R6.

Examples 1 to 8, 12 to 14, 18 to 25, 33 and 36 have an MIC of less than or equal to 1μg/ml against one or more of the above range of gram positive and gram negative bacteria.

Examples 11, 17, 26 to 32, 34 and 35 showed an MIC of less than or equal to 16μg/ml against one or more of the above range of gram positive and gram negative bacteria.

Examples 9, 10, 15 and 16 showed an MIC of less than or equal to 64μg/ml against one or more of the above range of gram positive and gram negative bacteria.